REMARKS

I. Status of claims

Claims 1-4, 7-16, 20-27, and 30-44 are pending. Claims 39-44 remain withdrawn and claims 5, 6, 17-19, 28 and 29 remain cancelled. Claim 1 has been amended to overcome the 35 U.S.C. § 101 rejection. Support for this amendment may be found in FIG. 2 and paragraphs [0026] and [0050]-[0053] of the specification. Claims 1, 16 and 27 have been amended in this response to clarify the claimed invention. No new matter has been added through these amendments.

II. Claim objections

The examiner has objected to claims 1, 16, and 27 because, according to the examiner, these claims would be more precise if (a) the preposition "in" in the phrase "point in the" was exchanged with "of," and (b) the term "fragment" was replaced with "fragments."

In this response, Applicants have amended claims 1, 16, and 27 to make these suggested changes. The amendments should overcome the examiner's objections to these claims.

III. Rejections under 35 U.S.C. § 101

The examiner has rejected claims 1-4 and 7-15 under 35 U.S.C. § 101, as being directed to non-statutory subject matter. Applicants have amended claim 1 to reflect that the process is a computer-based process with at least one step carried out using a computer processor. The amendment clarifies and emphasizes that the process is tied to a particular machine, in accordance with the test held in *In re Bilski* and in subsequent decisions. According to *In re Bilski*, the appropriate test for 35 U.S.C. § 101 eligibility focuses on whether a process is "tied to a particular machine or apparatus or if it transforms a particular article into a different state or thing." The claimed invention meet this test.

Transformation is involved in the manipulations of the molecules (which are particular articles) through the providing, decomposing, introducing, and coupling steps. Additionally, the amended claims tie the method to a particular machine, namely a computer processor, which is fundamentally involved with carrying out the calculating the intermolecular interaction energy. Thus, the process is tied to a particular machine as well as to a transformative process.

Accordingly, Applicants request that the examiner withdraw the rejection of claim 1 and claims 2-4 and 7-15 under 35 U.S.C. § 101.

IV. Rejection under 35 U.S.C. § 103(a) over Amovilli in view of Novosadov

The Examiner has rejected claims 1-4, 8-13, 16, 20-25, 27, and 31-36 under 35 U.S.C. § 103(a) as being unpatentable over 2002 Journal of Chemical Physics article by Amovilli *et al.* ("Amovilli") in view of 1993 Journal of Structural Chemistry article by Novosadov *et al.* ("Novosadov"). Applicants respectfully traverse this rejection.

According to the examiner, Amovilli discloses methods of calculating intermolecular interactions energies of large molecules based on a fragmentation scheme in that a first molecule is decomposed into at least two fragments, the right and left sides of decomposition points are both capped with an atom, and the first molecule is modeled as a sum of the capped fragments minus the contribution of the pair of caps. The examiner states that the contribution of the pair of caps is shown in equation 1 as $-H_a - H_b$, which represents the individual caps. The examiner further states that in eqn. 3 the contribution from the caps is summed and the total subtracted from the total interaction energy of the molecular portion. Novosadov is stated to disclose the advantage of fragmenting large molecular system into small fragments for quantum mechanical calculations in that it economizes computer resources and enables one to handle a molecular system of any complexity. Applicants respectfully traverse this rejection.

The claimed invention relates to a method for calculating intermolecular interactions energy between two molecules involving the steps of decomposing a first molecule into two or more molecular fragments; introducing one or more pairs of conjugate caps at each decomposition point of the molecular fragments; coupling each pair of conjugate caps to form one or more coupled caps; determining the interaction energies (a) between each molecular portion and a second molecule, and (b) between each pair of coupled caps and the second molecule; and calculating the intermolecular interaction energy between the first molecule and the second molecule based on the interaction energies determinations.

While Amovilli discloses methods of calculating intermolecular interactions energies of large molecules based on a fragmentation scheme, Amovilli fails to teach the *coupling of caps* before calculating the interaction energy between the caps and a second molecule. Additionally, Amovilli fails to teach determining the interaction energy between each pair of *coupled caps* and

the second molecule. These two claim elements are neither taught nor suggested anywhere in the Amovilli disclosure.

Instead, Amovilli states that if the A and B fragments are linked by a single σ bond (sigma bond), the effects of the A-B bond on X (the second molecule) is considered equivalent to that of an A-H bond plus a B-H bond minus the contribution of two intruder hydrogen (cap) atoms. See page 3004, column 2. In other words, each cap's intermolecular interaction energy is individually measured without the two caps being coupled together first. In eqn. 3, Amovilli further shows that contribution from the caps is individually subtracted without the two caps being coupled together first when calculating the total interaction energy of the molecular portions.

Amovilli's method has additional drawbacks. By capping only with hydrogen atoms, only certain molecular fragments may be capped in a manner where the cap would reasonably replicate the desired chemical environment. For practical reasons, capping with hydrogen is therefore very limited. Applicants' claimed invention allows for the caps to be any molecule that mimics the original molecular part being cut away. See paragraph 40. A wide range of molecular caps can be used because the interaction energy from whatever cap is being used may be accounted for under the process of coupling the caps together and determining the interaction energy of the coupled caps.

The interaction energy of the coupled caps (i.e. the conjugate cap interaction energy) can then be factored into the equation for calculating the intermolecular interaction energy, for instance by subtracting the conjugate cap interaction energy from the interaction energy of the molecular portions (see claim 9). Because Amovilli does not couple of the caps together, the conjugate cap interaction energy is not calculated or even accounted for under the Amovilli method. This essentially limits the caps Amovilli can use to hydrogen while at the same time limiting Amovilli's method to molecular fragments that are suitable to be capped with hydrogen.

Applicants' method of coupling of the caps and determining the intermolecular interaction energy of coupled caps thus represents an improved, more rationale, and more flexible method of calculating the intermolecular interaction energy of the molecule.

Novosadov, the secondary reference cited by the examiner, suffers from the same shortcomings as Amovilli. The examiner relies on Novosadov for disclosing the advantage of fragmenting large molecular system into small fragments for quantum mechanical calculations.

Novosadov, however, makes no disclosure with regard to coupling the caps together or determining the interaction energies of the coupled caps. When joining the fragments together, Novosadov, similarly to Amovilli, focuses on hydrogen atoms and treats the hydrogen atom caps separately. See page 31. Novosadov thus fails to overcome the deficiencies identified in Amovilli.

Accordingly, Amovilli and Novosadov, taken alone or in combination, fail to teach or suggest Applicants' claimed invention. Applicants respectfully request that the rejection under 35 U.S.C. § 103 (a) be withdrawn.

V. Rejection of claims 7, 14, 15, 26, 30 and 38 under 35 U.S.C. § 103(a)

Claims 7 and 30 have been rejected under 35 U.S.C § 103(a) as being unpatentable over Amovilli in view of Novosadov as applied to claims 1-4, 8-13, 16, 20-25, 27 and 31-36 and further in view of 1992 Computer, IEEE article by Shivarati *et al.* ("Shivarati"); claims 14 and 37 have been rejected under 35 U.S.C § 103(a) as being unpatentable over Amovilli in view of Novosadov as applied to claims 1-4, 8-13, 16, 20-25, 27 and 31-36 , and further in view of 2001 Journal of Computer-aided Molecular Design article by Ewing *et al.* ("Ewing"); and claims 15, 26, and 38 have been rejected under 35 U.S.C § 103(a) as being unpatentable over Amovilli in view of Novosadov as applied to claims 1-4, 8-13, 16, 20-25, 27 and 31-36, and further in view of 1999 Journal of Physical Chemistry A article by Ante *et al.* ("Ante").

Applicants respectfully traverse these rejections. None of the secondary references relied upon by the examiner overcome the deficiencies of Amovilli and Novosadov, as discussed below.

The examiner relies on Shivarati for disclosing distributed computing systems. However, using the distributed computing system of Shivarati would not lead one of ordinary skill in the art to couple the caps together before calculating the interaction energy between the caps and a second molecule, as recited in Applicants' claimed invention.

The examiner relies on Ewing for disclosing that molecular interaction energies can be calculated between a first molecule that is protein or peptide and a second molecule. However, Ewing does not teach or suggest fragmentation and capping of macromolecules, e.g. protein or peptide. On the contrary, Ewing focuses on the incremental construction of the second molecule, e.g. the drug. Ewing is using an anchor-and grow approach to dock a small molecule onto a

macromolecule. In the anchor-and-grow approach, interaction energy between the anchor point (part of the small molecule) and the macromolecule is minimized first. The anchor is grown a little bit by addition of next part of the small molecule and the energy between the so grown anchor and macromolecule minimized. This growing and minimization steps are repeated until the molecule is fully assembled. See Figure 1 on page 412. Thus the final intermolecular interaction energy between the two molecules is not based on fragmentation of the larger molecule, as recited in Applicants' claimed invention.

Furthermore, Ewing's anchor-and-grow approach does not involve capping of the growing anchor. Nor would Ewing's method lead one of ordinary skill in the art to couple the caps together. Applicants also submit that examiner is mistaken in asserting that Ewing teaches that water is used as second molecule. Ewing includes water as part of the active site of the macromolecule, but does not calculate interaction energy between the water molecules and the macromolecule. For all intents and purposes, these water molecules are part of the larger molecule.

The examiner relies on Ante for disclosing CH_3 caps. In Ante, molecules are decomposed so that different energy calculation algorithms can be applied to the different parts. Similarly to Novosadov above, Ante is calculating the ground state energy of a single molecule, not the intermolecular interactions energy between two molecules, as recited in Applicants' claimed invention. Furthermore, no allowance for contribution from the caps is made. See Eqn. 1, page 9291. Thus, even using Ante's methyl caps, there is no teaching or suggestion that the caps be coupled or that the conjugate cap interaction energy be determined and used to calculate the intermolecular interaction energy.

Accordingly, Amovilli, Novosadov, Shivarati, Ewing and Ante, taken alone or in combination, fail to teach or suggest the claimed invention. Applicants respectfully request that the rejections under 35 U.S.C. § 103 (a) be withdrawn.

VI. Conclusion

In view of the above amendments and remarks, Applicants respectfully request reconsideration of this application.

Except for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this

application including fees due under 37. C.F.R §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 19-2380. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. §1.136(a)(3).

Respectfully submitted,

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